Intrinsic Subtypes Clinical Study Portfolio

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Questions

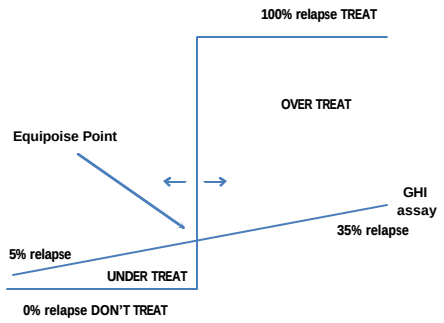
Can the PAM50 be used regarding chemotherapy versus no chemotherapy in the setting of low ROR Luminal A breast cancer?

Does intrinsic subtype drive treatment choice in high risk patients?

Does the intrinsic subtype displace current approaches to biomarker analysis in breast cancer (Grade, ER, PgR and HER2)?

When to sample? Before or after an estrogen deprivation challenge?

Decision Making Tools – a long way to go



Retrospective Questions

- "Pure" Prognosis
- 1000 node negative cases from Wash U contribution to CBCTR
- Status: samples undergoing processing
- "bake off" between qPCR and non qPCR technologies (nanostring and array based) under consideration.
- Comparisons with standard assays

Retrospective Questions

- Value of anthracycline vs CMF
- Several trials identified for possible analysis
- MA5 – concept in preparation (but sample numbers denuded by multiple biomarker analysis)
- 89D – concept approved by Danish Cooperative Group

D89

BACKGROUND: Previous analyses of TOP2A and HER2 in the Danish Breast Cancer Cooperative Group (DBCG) trial 89D suggested that TOP2A amplifications and possible also deletions are predictive markers for the effect of adjuvant epirubicin in patients with primary breast cancer. We present an updated and extended statistical analysis, requested for IVD-labeling of TOP2A testing.

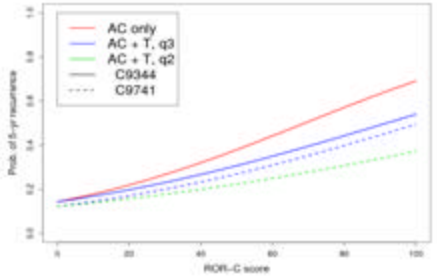
MATERIAL AND METHODS: **In the DBCG trial 89D 980 Danish patients were randomly assigned to nine cycles of intravenous CMF (cyclophosphamide, methotrexate, and fluorouracil) or CEF (cyclophosphamide, epirubicin, and fluorouracil).** Archival tumor tissue was collected retrospectively from 806 of these patients in a prospectively designed, biological sub-study, and was successfully analyzed for TOP2A aberrations and HER2 status in **773 samples (96%).** Recurrence-free survival (RFS) was the primary endpoint. RESULTS: TOP2A aberrations (amplifications and deletions) were significantly associated with shorter RFS (p<0.0001) and overall survival (OS) (p<0.0001). Deleted cases had worse prognosis than amplified cases. In a Cox proportional hazard model TOP2A was an independent prognostic marker for RFS and OS. Patients with amplifications had a 61% reduction in the risk of an event (p=0.002) and a 51% reduction in the risk of death (p=0.01) if allocated to CEF compared to 6% and 10% in TOP 2A normal patients. A similar but non-significant trend (p=0.08) was shown in patients with TOP2A deletions. Clear statistical evidence of a differential benefit, favoring CEF among patients with TOP2A aberrations was found for RFS (p=0.02 for interaction) but not for OS (p=0.14 for interaction).

CONCLUSION: In conclusion, this updated analysis of TOP2A aberrations in DBCG trial 89D suggests a differential benefit of adjuvant chemotherapy in patients with primary breast cancer, favoring treatment with epirubicin in patients with TOP2A amplifications, and perhaps deletions. Additional studies are needed to clarify the exact importance of TOP2A deletions on outcome, but deletions have proven to be associated with a very poor prognosis.

Retrospective Questions

- Value of taxanes as adjuvant therapy
- Several large trials addressing the value of a taxane under consideration by cooperative groups
- C9344 – concept submitted
- GEICAM 9906 (FECq3w thenTq3wx8 or FECq3x6 – concept approved, contract in process.

Modeling Taxane and dose dense Benefit



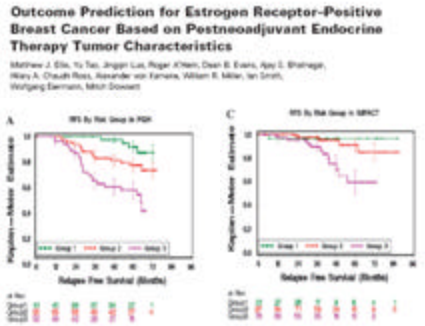
Retrospective Questions

- Value of endocrine therapy
- MA12 under analysis (412 samples)
- BIG 1-98 concept submitted (may need a case control design)

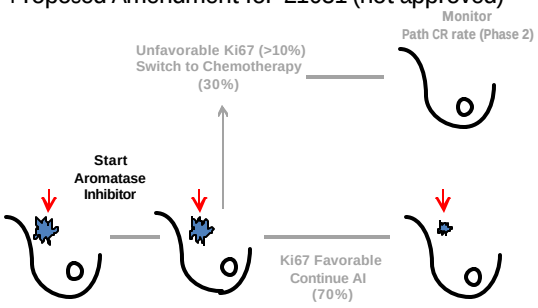
Retrospective Questions: Defining spectrum of investigational drug sensitivity in "true basal" breast cancer

PARP inhibitor
Cetuximab
Bevacizumab
Carboplatin

When to take a sample to obtain the intrinsic subtype?


Outcome Prediction for Estrogen Receptor-Positive Breast Cancer Based on Postneoadjuvant Endocrine Therapy Tumor Characteristics

Proposed Amendment for Z1031 (not approved)



One month biopsy with Ki67 analysis CLIA lab analysis with (DC Allred, cross validated with M Dowsett)